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Utility of Bone Marrow Culture and Biopsy in the Diagnosis of Disseminated Infections in AIDS

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Bone marrow examination (BME) has been used as a diagnostic test of last resort in HIV infected patients. Identifying factors that would increase the diagnostic yield of BME would be useful. A retrospective cohort study was done to determine the predictive value of BME for disseminated infection in 133 patients with HIV infection in a 4-year period at an active HIV clinical center. Thirty-two percent of the cases had evidence of a disseminated infection on BME but only 10% of cases had a diagnosis made exclusively by BME. Multivariate analysis demonstrated that a positive result was more likely in those patients with fewer than 50 CD4 cells/mm^3 and those with a hematocrit of less than 25% ($P < 0.01$). BME can be a useful, low-risk diagnostic procedure in selected patients with HIV infection who are ill with a low CD4 count and/or have a hematocrit less than 25%. A diagnosis can usually be made by other means, suggesting that this test should be limited to those in whom other diagnostic modalities have been exhausted. Am. J. Hematol. 56:1–4, 1997.

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INTRODUCTION

HIV infection is often complicated by opportunistic infections that infiltrate the bone marrow. Bone marrow examination (BME) via aspiration and core biopsy can identify such diverse infections as *Leishmania donovan, Pneumocystis carinii,* and *Penicillium warneffi* [1–5]. More commonly, infections such as *Mycobacterium avium complex (MAC), Mycobacterium tuberculosis,* and *Histoplasmosis capsulatum* are diagnosed through BME [6–11]. It is a high-yield procedure, providing evidence of infection in up to 42% of patients tested, and has a very low complication rate [6–10]. BME can provide microscopic diagnostic information before less invasive methods such as blood cultures [9,11]. In some cases, BME can yield the only diagnostic material obtained from a patient.

Despite these potential advantages, BME may have limited diagnostic utility. In a retrospective study of 65 HIV-infected patients, Engels et al. found the diagnosis was made by other modalities in almost all the cases that had a positive BME [11]. These results were available before the results of the bone marrow were known in almost one-half of those patients. In addition, BME sometimes provides inconclusive results and it is considered a painful invasive test, despite a low complication rate. Thus, identification of those patients in whom BME could provide unique diagnostic information would be a study of considerable merit. We performed a retrospective study of all the HIV-infected patients at U.T. Southwestern Medical Center who had undergone BME in order to correlate the pathologic and culture results of BME with clinical parameters, which might predict patients likely to have diagnostic BME.

METHODS

All patients with HIV infection who had undergone a bone marrow biopsy with culture from 1989 to 1993 at Parkland Memorial Hospital, Dallas, Texas, were identified through the University of Texas Southwestern Medical Center clinical HIV research database. Hospital charts of these patients were reviewed for clinical findings including fever, hepatomegaly, and splenomegaly; laboratory results of CD4 count, hematocrit, platelet count, absolute neutrophil count, alkaline phosphatase, AST and gamma glutyl transferase, pathologic results of bone marrow biopsy including the presence of acid fast bacilli, fungal elements, and granuloma; and culture results of blood and bone marrow aspirates.

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TABLE I. Summary of Positive Bone Marrow Results

	Percent positive (N = 133)
Bone marrow culture	
Mycobacterium avium complex	16.5 (22)
Histoplasmosis capsulatum	4.5 (6)
Mycobacterium tuberculosis	0.8 (1)
Aspergillus fumigatus	0.8 (1)
Pathology	
Granuloma	21 (28)
Acid fast bacilli	12 (16)
Fungal elements	1.5 (2)
Definitive diagnosis by bone marrow	22.5 (30)
Unique diagnosis by bone marrow	10.5 (14)
Total positive bone marrows	32 (43)

TABLE II. Potential Markers for Positive Bone Marrow Aspirate and Biopsy

Predictor	Odds ratio	95% C.I.
Univariate analysis		
Temperature >38.5	1.9	0.8–4.5
Hepatomegaly	1.1	0.18–7.1
Splenomegaly	3.5	0.8–15.8
<50 CD4 cells/mm^3	3.5	1.4–8.7
Absolute neutrophil count <1,000 cells/mm^3	1.1	0.42–2.7
Hematocrit <25	3.4	1.4–7.8
Alkaline phosphatase >180 I.U.	2.1	0.6–7.0
GGT >300	2.7	0.75–10.0
Multivariate analysis		
Temperature >38.5	1.3	0.5–3.0
Splenomegaly	3.6	0.7–17.2
CD4 <50 cells/mm^3	3.1	1.2–7.6
Hematocrit <25%	2.9	1.2–6.5
GGT >300	1.8	0.4–6.7

Bone marrow aspirates and biopsies were considered positive if a culture of the aspirate grew a significant pathogen, or if there were granulomata, fungal elements, or acid fast bacilli on pathologic examinations. Results of bone marrow aspirates and biopsies were compared to blood cultures to see if the bone marrow results provided new or unique diagnoses that could not be obtained through blood cultures. The results of bone marrow biopsy were compared to results of cultures of bone marrow aspirates to determine if pathologic results could predict specific infections. Similarly, clinical findings and laboratory test results in patients with positive bone marrow examinations were compared to those in patients with negative bone marrow examinations to identify the clinical features associated with infection in the bone marrow.

Association between pathologic results and bone marrow cultures were determined through the Chi-Squared test or Fisher's Exact Test where appropriate. Identification of clinical features associated with positive bone marrow aspiration and biopsy was performed by the Chi Squared Test or Fisher's Exact Test for categorical variables and by the Student's *t*-test for continuous variables. Continuous variables were dichotomized where clinically significant (i.e., CD4 count, HCT, ANC) at one-half the difference between the means of the two groups (i.e., alkaline phosphatase or GGT). Multivariate analysis was performed by logistical regression.

RESULTS

One hundred and thirty-three patients who underwent bone marrow aspiration and biopsies were identified. Results of bone marrow examinations are summarized in Table I. Cultures of the bone marrow aspirates were positive for pathogenic organisms in 30 patients, providing a definitive diagnosis in 22.5% of the procedures. The majority of the organisms isolated were *Mycobacterium avium complex* (22), followed by *Histoplasma capsulatum* (6), *Mycobacterium tuberculosis* (1), and *Aspergillus fumigatus* (1). Pathologic examination showed evidence of infection in 30 patients, including granuloma (28), acid fast bacilli (12), or fungal elements (2). Bone marrow examination provided a unique diagnosis in only 14 patients or 10% of the procedures performed. None of the patients who had a diagnosis of systemic infection such as *Mycobacterium avium complex* or *Histoplasma capsulatum* had a second organism isolated on BME. Each bone marrow was well tolerated and there were no reported complications.

Pathologic findings were predictive of disseminated infections. Patients with granulomata were 4.1 times more likely to have a positive culture than those without granulomata ($P < 0.001$); while patients with acid fast bacilli were 4.8 times more likely to have positive bone marrow cultures ($P < 0.001$). All but one of those infections were with *Mycobacterium avium complex.* Despite the small number of patients with fungal infections, those with fungal element on bone marrow biopsy were 26 times more likely to have a fungal infection than those without fungal elements ($P = 0.002$).

Potential predictors of positive bone marrows are summarized in Table II. Univariate analysis identified less than 50 CD4 cells/mm^3 (OR = 3.5, $P = 0.005$) and less than 25% hematocrit (OR = 3.4, $P = 0.002$) as significant predictors of a positive bone marrow determination. There was a trend toward an increased chance for a positive bone marrow result ($P < 0.15$) in patients with fever, splenomegaly, or elevated gamma glutyl transferase. Patients with hepatomegaly, neutropenia, or elevated alkaline phosphatase did not have an increased chance of a positive bone marrow. Multivariate analysis by logistical regression demonstrated an increased likelihood for a positive bone marrow result in patients with a CD4 count less than 50 (OR = 3.1, $P = 0.013$) or with a hematocrit less than 25% (OR = 2.9, $P = 0.01$). In patients with splenomegaly, there was a trend toward

increased chance of a positive finding on BME (OR = 3.6, $P = 1.0$).

DISCUSSION

We found evidence of infection on BME in 32% of cases and made a microbiologic diagnosis in 22.5% of the procedures performed. When we examined the relationship of BME to peripheral blood culture, however, we found BME to be less useful. BME was positive prior to peripheral blood cultures in 4 cases and was positive in the face of negative blood cultures in 10 cases, providing a unique diagnosis in only 10% of the procedures performed. The retrospective nature of this study may effect the yield that was observed for BME. There was a bias toward performing this test in patients without a diagnosis of disseminated infection because patients in whom a diagnosis was made by less invasive means would be less likely to undergo BME. Another potential bias is the fact that all of the subjects had a unilateral bone marrow aspiration and biopsy. A second procedure could increase the yield although this is not likely. In a small prospective study of BME in HIV-infected patients with MAC, the yields were similar for each side when bilateral bone marrow biopsy was performed [12]. Despite these potential biases, our results are remarkably similar to those reported in the literature where diagnostic yields of BME range from 25 to 42% [6–11]. Similarly, Engels et al. found that BME provided a diagnosis more rapidly or equally in 14% of febrile HIV infected patients [11].

We also examined the relationship between pathology found on BME and microbiologic diagnosis. Patients who had either granulomata, acid fast bacilli, or fungal elements on bone marrow biopsy were 4 times more likely to have a disseminated infection than those who did not have these features on BME ($P < 0.001$). Granulomata or acid fast bacilli were most often associated with infection with *Mycobacterium avium complex* (MAC). Similarly, fungal elements were predictive of a disseminated fungal infection. However, none of the patients with granuloma on BME had fungal infection. Others have found poorly formed granuloma in subjects with disseminated histoplasmosis [9]. Despite these associations, pathologic results of BME were not always diagnostic as 12 patients with granuloma and acid fast bacilli on BME never had a microbiologic diagnosis. It is perhaps possible that these 12 patients had disseminated MAC given the high prevalence of MAC in our series. The local prevalence of MAC, *Mycobacterium tuberculosis*, or systemis mycoses, however, can alter the predictive value of pathologic findings on bone marrow biopsy.

We compared clinical features of patients with positive BME to those with negative BME to identify those features that would help clinicians identify patients who might benefit from BME. In a multivariate analysis, we found that patients with fewer than 50 CD4 cells/mm^3 or a hematocrit less than 25% were more likely to have a positive bone marrow result. The association between low CD4 counts and positive BME is not surprising as most of the infections identified in this series occur in individuals who were highly immunosuppressed. Similarly, anemia was often found in association with the infections identified in this series. Interestingly, neither neutropenia nor abnormal hepatic enzymes, previously described features of disseminated MAC or histoplasmosis in HIV, were predictive of a positive BME result. Thus, these predictors provide little guidance as to in whom to perform a BME, as anemia and low CD4 count are well-described predictors of disseminated infection in patients with AIDS.

CONCLUSIONS

We conclude that BME has limited value in the diagnosis of disseminated infection in AIDS patients. Although the diagnostic yield is relatively high, unique diagnosis was obtained in only 10% of the procedures performed. Timing of this procedure is clearly an issue. If on a clinical basis, a patient appears acutely ill with a disseminated infection, early BME may be indicated to guide empiric therapy given the positive predictive value of granuloma or fungal elements on pathologic exam. If initiation of therapy is not urgent, then other more cost-effective procedures may be utilized instead. In general, we recommend that less invasive procedures, such as blood culture for mycobacteria and fungi and test for histoplasma antigen, should be done initially. If these tests are negative, then BME may be an appropriate procedure in those patients with end-stage AIDS and anemia in whom no other diagnosis was found.

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